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Original Article

Gel Formulation and an In-vitro Kinetic Permeation Release Study of Cefixime Trihydrate and Chlorpheniramine Maleate (CCM)

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ABSTRACT

Cefixime is an antibiotic drug used to treat infection. Chlorphenamine, also known as chlorpheniramine, is an antihistamine and used to treat allergic diseases such urticarial infections and rhinitis **Objective:** To formulate a gel by using propylene glycol (PG) along with Polyethylene glycol (PEG) in order to enhance the percutaneous absorption and release of cefixime trihydrate and chlorpheniramine maleate from TDDS (transdermal drug delivery system). **Methods:** Various formulations (G1 to G13) containing cefixime trihydrate and chlorpheniramine maleate gels (CCM gels) were prepared for this purpose with PG and PEG in different ratios. Firstly, gel optimization was estimated from the physical properties of the gels. Later, the diffusion process was carried out through Franz diffusion cells to find out the permeation kinetic parameters of these gel formulations. Only two of the gels (G1 and G3) were selected for further process while the rest were not employed due to stability issues. **Results:** The obtained results were analyzed by using statistical RSM (response surface methodology) and the link between the independent and response variables was depicted using contour plots. The result of the current study of both these gels indicated high values of flux and ER (enhancement ratio) while a reduction in tlag value. However, no significant difference was seen in the values I/R (input ratio) and Kp (permeation constant) with other formulated gels. **Conclusions:** It was concluded that the addition of PG and PEG into gels could enhance the permeation of cifixime trihydrate and chlorphenaramine mleate across membrane.

INTRODUCTION

Cefixime is an antibiotic drug used to treat infection. It belongs to the class of 3rd generation cephalosporin.It is stable to the hydrolysis of β-lactamases [1]. Chlorphenamine, also known as chlorpheniramine, is an antihistamine that is frequently sold in the form of chlorpheniramine maleate (Chlorphen-12). It is used to treat allergic diseases

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such urticarial infections and rhinitis [2]. Intensive research is being conducted to examine alternative ways for improving drug delivery. Various studies are being conducted in order to examine several tactics to facilitate drug delivery [3]. Certain novel ways involve the incorporating drug into microcapsules, niosomes, nanocapsules, emulsion-based systems, liposomes, along with the use of several combinations of chemical enhancer [4]. Chemical enhancers are compounds that weaken the skin's barrier function briefly, allowing for greater medication absorption. Some examples of them include crucial terpenes, fatty acids, and oils. Several in-vitro investigations showed that polyethylene glycol (PEG) when used in combination with propylene glycol (PG) may effectively penetrate the skin, building on their ability as skin permeation enhancers [5]. This study was conducted to assess penetration and release kinetics of medication in the form of CCM gel by using Response Surface Methadology through Franz diffusion cells by using silicone membrane [6]. A technique called Response Surface Methodology (RSM) was adopted in order to develop a CCM gel comprising cefixime trihydrate and chlorphiniramine maleate in various ratios in association with permeation enhancers such as PG as well as PEG [7].Permeation tests were carried out utilising full thickness silicone membrane in modified Franz diffusion cells to study saturation and drug release kinetics from produced gels. Cefixime, a 3rd generation antibiotic is freely soluble in methanol and may quickly traverse the skin or membranes, even when administered in small amounts. In contrast, CPM is freely soluble in both methanol and water, but due to the mixture of organic solvents, both can have a significant influence [8]. Permeation tests were carried out utilising full thickness silicone membrane in modified Franz diffusion cells to study saturation and drug release kinetics from produced gels [9], as a result, this type of gel formulation might become more important and directly apply to topical infections in order to solve this problem. The primary goal to conduct this research study was to formulate a gel with a combination of antibiotic and antihistamine which can be effectively used in topical applications.

METHODS

Cefixime trihydrate (99.9 % purity) was acquired from Merck, Germany. Rest of the chemical substances which includes benzyl alcohol, carbopol 934, polyethylene glycol (PEG 1000), propylene glycol (PG), triethanolamine, rose mery oil, ethylene glycol, and methanol, which were consumed bought from Germany (Merck). UV-Spectro photometer (Spectronic, Genesys 5), Sonicator, Water bath, Weighing balance and Magnetic Stirrer/Hot Plate. CCM gels of cefixime trihydrate and chlorphenira mine maleate having differential ratios of PG & PEG was made by carefully weighing as well as measuring all of the materials, which had variable amounts of each. The CCM gel formulation required taking dilution solution of 5.5mL of methanol in conical flask and dissolving 0.2 g each of cefixime trihydrate and PEG and chlorphinaramine maleate were introduced with constant swirling on a magnetic stirrer with such a magnetic flea until entirely dissolved. In another separate conical flask PG was taken and benzyl alcohol was used to dissolve it. Then add 0.5 g of carbopol-934. Magnetic stirring was continued until the carbopol-934 was lump-free. The prepared form of the 1st conical flask medicines solution was added to the homogenized carbopol-934 preparation in the 2nd conical flask. PG under continuous magnetic stirring adds benzyl ethylene glycol as well as alcohol by portions with continuous stirring and isopropyl alcohol (IPA) was added continuously during preparation and required volume was adjusted through IPA. Finally added rose merry oil for fragrance and later kept it in collapsible tubes for using it later on. The compositions of different gels are mentioned in the following Table 1.

Table 1: Gels constitution

Sr. no	Cefixime trihydrate (g)	CPM (g)	X_1=Propylene glycol (g)	X_2=Poly ethylene Glycol (g)	Carbopol- 934 (g)	Benzyl alcohol (g)	EG (g)	Methanol (g)	Rose mery oil (g)	Volume make up with IPA (g) make 20 gm
Gel_1	0.2	0.2	4.4	1.9	0.5	3.138	0.11	5.9	0.3	3.52
Gel_2	0.2	0.2	4.8	1.9	0.5	3.138	0.11	5.5	0.3	3.352
Gel_3	0.2	0.2	4.4	2.1	0.5	3.138	0.11	5.5	0.3	3.552
Gel_4	0.2	0.2	4.8	2	0.5	3.138	0.11	5.5	0.3	3.25
Gel_5	0.2	0.2	4.2	2	0.5	3.138	0.11	5.5	0.3	3.85
Gel_6	0.2	0.2	5	1.8	0.5	3.138	0.11	5.5	0.3	3.25
Gel_7	0.2	0.2	4.6	2.2	0.5	3.138	0.11	5.5	0.3	3.25
Gel_8	0.2	0.2	4.6	2	0.5	3.138	0.11	5.5	0.3	3.75
Gel_9	0.2	0.2	4.6	2	0.5	3.138	0.11	5.5	0.3	3.75
Gel_{10}	0.2	0.2	4.6	2	0.5	3.138	0.11	5.5	0.3	3.75
Gel_{11}	0.2	0.2	4.6	2	0.5	3.138	0.11	5.5	0.3	3.75
Gel_{12}	0.2	0.2	4.6	2	0.5	3.138	0.11	5.5	0.3	3.75
Gel_{13}	0.2	0.2	4.6	2	0.5	3.138	0.11	5.5	0.3	3.75
Gel_c	0.2	0.2	0	0	0.5	4.64	0.11	7.86	0.3	6.23

Diffusion research was conducted using Franz diffusion cells with a diffusional area of 0.788 cm2 as well as a receptor phase of volume 5 ml across a silicone membrane. Silicone membrane had been trimmed to size in a circular form and immersed overnight in the methanolic solution. After that, the membrane was put inside the diffusion cells' donor and receptor compartments. The vacuum grease was applied between the surfaces of collar of both the sections before the membrane was put in place to prevent

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it from leakage. Once the donor compartment was placed over the receptor compartment, they were clamped. The arm of the cell was used to inject the receptor fluid into the receptor compartment, which was later withdraw in a bath (ultrasonic) to get rid of any air bubbles and avoid air pockets from accumulating in the receptor phase. In the receptor compartment, a magnetic stirring bar was placed in order to maintain constant mixing of the receptor phase. Then, to prevent evaporation, a parafilm was placed over the donor's perimeter and the receptor's cell arm aperture. The diffusion cells were used to maintain the surface temperature of membrane by placing it on a moving bed that was submerged in water bath set fixed at temperature at 37 °C. After 1 hour, the receptor phase was entirely withdrawn and then completely filled with receptor fluid. Test solution (1ml) placed inside the donor chamber. (cefixime trihydrate and chlorphiniramin maleate, Using a micropipette, sample solution (0.2ml) was taken from the receptor solution at predetermined intervening time of 15 min, 30 min, 45 min, 60 min, 90 min, 120 min and 180 min. To keep the receptor compartment in the sink condition, when every sample was taken then receptor fluid (0.2ml) was added. To determine permeated amount through the silicon membrane, the samples were spectrophotome trically examined at 254 nm and 265 nm. Experiments were conducted in three sets. For solubility analysis, a large quantity of pure cefixime trihydrate was added to three separate glass bottles holding five millilitres each of Phosphate buffer, methanol and distilled water. These combinations were stirred for 48 hours at a constant temperature of 37± 1°C with a thermostatically-controlled stirrer. Centrifugations of mixtures were done for 30 min at 4000 rpm. An aliquot of the supernatant was then removed using a pipette, and the concentration in g/mL was calculated using a UV spectrophotometer at 254 nm. The optimal solvent system for the receptor phase was therefore determined by studying solubility in each solvent. The partition coefficient of Cefixime trihydrate was determined by dissolving it in 10mL of water in separating funnel after shaking it for 10 minutes. Then, after adding 10 mL of octanol solution, the funnel was vigorously shaken for further 10 minutes and then placed it for 1 day. Each layer was separated into two layers, collected in a test tube, and then analyzed it in UV Spectrophotometer to determine the octanol / water ratio. Experiments were conducted in three sets (n=3). Several RSM approaches for this optimization study were executed using Design Expert® software 8.0.1. The most effective gel formulation was found using a computer RSM that used polynomial equations to estimate the impact of formulation factors on drug invasion via membrane as shown in Figure 1. These designs were taken from CCD with α = 2. The ratios of Propylene glycol and Poly ethylene glycol were evaluated at five levels. However, the central point was considered in four times.

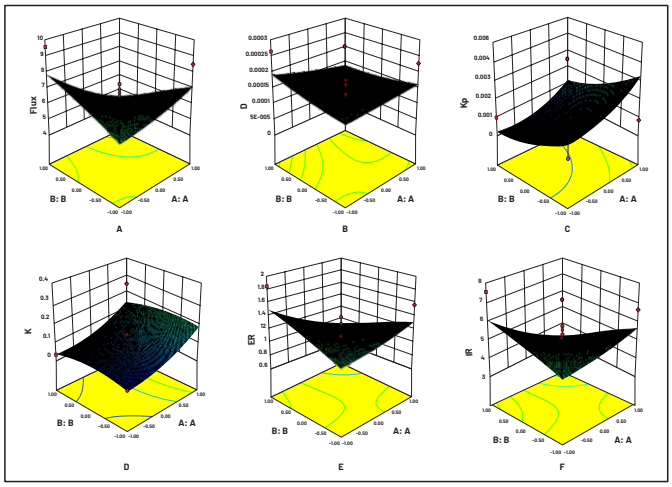

Figure 1: Representing the contour plots of CCM gel formulations obtained by RSM

Parameter like Viscosity was determined through Brookfield viscometer. All the measurements were taken at room temperature at 25°C. pH of CCM gels were calculated at 25 °C by using digital pH meter. Physical traits of formulated CCM gels, such as transparency, precipitation, and homogeneity, were also observed. Overall, 13 experimental turns for CCM gels were created with CCD (two-factor) run for 7 responses as shown in Table 5. We packed CCM gels in collapsible aluminum tubes weighing (5 g) which were exposed so that it can be tested for stability studies at 25 °C at 60 % RH and 40 °C at 65 % RH for 3 months. Specimens were held for the designated amount of time before CCM gels were analyzed for their rheological characteristics, physical appearance, and chemical assays.

RESULTS

Cefixime trihydrate is sparingly soluble in water, however it is easily soluble in two solvents: methanol and IPA. Contrary, CPM was readily soluble in both methanol and water. Two optimized CCM gels, G1 and G3 were used for stability studies which were found stable under specified storage environment. The solubility of CCM gel's in water was 1.28 mg/mL, in methanol 1.95 mg/mL, in PBS (phosphate buffer solution) was 0.821 mg/mL whereas in methanol water (2:1), the solubility reached to 72.15 mg/mL. However, the partition coefficient (Ko/w) was 3.68 ± 0.11 that was associated to log P = 3.80 reported previously. Gels were observed for their physical properties like clarity, precipitation and consistency and were found to have homogenous, transparent and white crystallite appearance. Table 2 showed measured values of drug content, pH, viscosity, spread ability and consistency of CCM gels while Table 3 indicated larger values of flux and ER

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for G1 and G3 whereas the values of tlag were quite minimum. Kp and I/R values were seem to be more prominent. Overall, indicating their ability to cross membrane in less time as compared to other formulated gels. Values of were also more prominent in G1 and G3. We selected both G1 and G3 gels for further in-vitro rat skin permeation studies to authenticate our outcomes. For this purpose, a primary test of skin irritation was conducted for volunteers with no irritation or lesions (erythema, redness and urticarial) seen during 1 month trial. For analysis of stability, the optimized CCM gels were kept for three months in accordance with ICH norms at 25.0 ± 1 °C, at 60 % RH and 40 ± 1 °C, at 75 % of RH and were examined for a change in their appearance.

Table 2: Exhibiting the results of various kinetic parameter study of CCM

Formulation	Gel_1	Gel_2	Gel_3	Gel_4	Gel_5	Gel_6	Gel_7	Gel_8	Gel_9	Gel_{10}	Gel_{11}	Gel_{12}	Gel_{13}
Viscosity in m.poise	44	37	57	42	46	49	41	39	52	56	46	48	46
pH	3.92	3.76	3.84	3.87	3.94	3.94	3.95	3.97	3.94	3.96	3.91	3.94	3.92
Spread ability in cm	3.0	2.8	3.2	2.7	3.1	2.2	2.5	3.4	3.2	2.9	3.0	3.1	3.2
Clarity	YCT	YCT	YCT	YCT	YCT	YCT	YCT	YCT	YCT	YCT	YCT	YCT	YCT
Precipitation	N/ ppt	N/ ppt	N/ ppt	N/ ppt	N/ ppt	N/ ppt	N/ ppt	N/ ppt	N/ ppt	N/ ppt	N/ ppt	N/ ppt	N/ ppt
Drug content (%)	98.5	99.4	98.9	99.9	99.3	98.7	99.5	98.3	98.2	99.1	98.6	98.4	99.2
E/R/U (1st to day 30th)	0	-	0	-	-	-	-	-	-	-	-	-	-

Yellow Crystalline and Transparent (YCT), No precipitation (N/ppt), E: Erythema, R: Redness, U: Urticarial

Table 3: Permeation kinetic parameters of CCM gels through RSM

Sr. no.	t_{lag} (min) ±SD	Flux (µg/cm 2/min) ±SD	$D\times10^{-4}$ (Cm2 / min) ±SD	$K\times10^{-2}$ ±SD	$Kp\times10^{-3}$ (µg/cm 2/min) ±SD	ER ±SD	I/R (µg/ min) ±SD
Gel_1	17.745± 0.937	8.518± 0.026	2.290± 1.21E-05	3.3± 0.001	0.852± 0.002	1.556	6.720± 0.021
Gel_2	7.043± 0.083	5.363± 0.009	0.909± 1.08E-06	5.2 ± 0.001	0.536± 8.54E-07	1.039	4.231± 0.007
Gel_3	20.652± 0.165	9.560± 0.010	2.666± 2.13E-06	3.2± 0.001	0.956± 1.01E-06	1.852	7.543± 0.008
Gel_4	14.902± 0.211	5.015± 0.017	1.92± 2.72E-06	2.3± 0.001	0.502± 1.71E-06	0.971	3.957± 0.013
Gel_5	10.398± 1.464	6.649± 0.019	1.342± 1.89E-05	4.4± 0.001	0.665± 1.86E-06	1.288	5.246± 0.014
Gel_6	8.806± 0.303	5.653± 0.017	1.14± 3.92E-06	43.8± 0.001	5.656± 1.69E-06	1.095	4.463± 0.013
Gel_7	9.931± 0.126	4.804± 0.008	1.263± 1.63E-06	3.30± 0.001	4.804± 8.39E-07	0.931	3.791± 0.007
Gel_8	12.175 ± 0.204	5.116± 0.002	1.57± 2.63E-06	2.9± 0.001	0.512± 2.08E-07	0.991	4.037± 0.002
Gel_9	13.531± 0.147	6.738± 0.014	1.75± 1.9E-06	3.4± 0.001	0.673± 1.4E-06	1.305	5.316± 0.011
Gel_{10}	12.458± 0.266	7.258± 0.008	1.61± 8.08E-07	4.0± 0.001	0.726± 8.08E-07	1.406	5.726± 0.006
Gel_{11}	11.609± 0.489	4.306± 0.007	1.5± 6.32E-06	2.5± 0.001	0.431± 6.93E-07	0.835	3.397± 0.006
Gel_{12}	7.842± 0.243	4.051± 0.008	1.01± 3.14E-06	35.2± 0.001	4.051± 8.08E-07	0.785	3.197± 0.006
Gel_{13}	12.454± 0.263	7.254± 0.002	1.59± 3.4E-06	4.2± 0.011	0.728± 2E-07	1.402	5.695± 0.002

DISCUSSION

The mammalian skin layer stratum corneum selectively behaves as permeable membrane. Lipid molecules can be located to diffuse easily among keratinocytes [10]. These lipid intercellular molecules can be seen to dissolve easily in PG and PEG. PG and PEG affect is concentration dependent. The efficiency of PG is increased by adding more amount of PEG when both are used in combination. So, they have synergistic effect [11]. Earlier studies demonstrated how effectively PEG and PG have used to enhance the skin permeability [12]. In this study, the combined effects of PG and PEG as to increase permeability of skin was investigated, and several gels containing PG and PEG in various ratios were made using cefixime trihydrate and CPM. Free water in the tissue facilitates penetration and alters the drug's solubility in the stratum corneum (SC), which changes the drug's partition value from the vehicle into the membranes [13]. Hydration of SC enhanced the penetration of both hydrophilic and lipophillic chracteristics. An improved SC hydration resulted in the expansion and opening of dense SC structures, which increased drug penetration. Pyrrolidones, sulfoxides (SO), simple terpenes and terpenoids, uread, fatty acids and esters, poly vinyl alcohol(PVA) and essential oils are additional CPEs that resemble glycerides and were once employed in a variety of topical and transdermal treatments [14]. Cefixime trihydrate (an antibiotic drug) while chlorpheniramine maleate (1st generation antihistamine) were used in combination for 1st time to treat the topical infections rhinitis, urticarial, acne, inflammation and redness [15]. This was the simple part of wide-ranging research studies approved to explore numerous methods for supporting drug delivery across skin. CCM gel's solubility in water was 1.28 mg/mL, in methanol 1.95mg/mL, in PBS was 0.821 mg/mL while in methanolic water (2:1), the solubility was 72.15 mg/mL. Partition coefficient (Ko/w) was 3.68, compared with a previous value of log P = 3.80 [16]. CCM gels remained clear, crystalline and transparent. No change in consistency, viscosity, homogeneity was observed. Due to greater flux and ER value, the drug contents were released from gels and permeated through skin. In CCM gels, the values for flux and ER were greater in G1 and G3, whereas tlag values for both gels were least indicating the time required by G1 and G3 to cross the membrane was less in comparison with formulated gels [17]. Kp& I/R also showed projecting values in G1 and G3 [18]. So both the gels G1 and G3 were optimized the best formulation. No skin irritation or lesions (erythema, redness and urticarial) was found upon application of optimized CCM gels (G1& G3) indicating a good sign of its safety. ICH norms were performed for stability testing [19],

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the optimized CCM gels (G1& G3) were provided with 3 months of storage conditions as per criteria (25.00 ± 1 °C, at 60 % RH & 40.00 ± 1 °C, at RH 75 %), but no change in their appearance was analyzed. The greater values of ER, flux and minimum values of tlag while prominent values of Kp, I/R of CCM gels gave protuberant clue that they are able to pass across the human skin barrier easily. A CCD statistical design with 7 responses was chosen for this study using design selected from the previous reported studies of topical formulations [20]. The values of 13 CCM gels responses along with independent variables were also being generated, from where; the independent x-axis variables were PG and PEG while dependent variable responses were on Y1to Y7 in 3 hrs. Improved drug stability and solubility with reduced lag time has also increased the degree of drug delivery to the outer membrane compartment [21]. Further this study also suggested that PG and PEG in combination has enhanced the rate of permeation of CCM gels in different ratios. frothy with targeted specific gravity then added in natural milk to form value added milk to get only substantial profit [10]. The analysis of different adulterants in milk samples showed such findings that helped in the discrimination of satisfactory and unsatisfactory milk samples through provided pure raw milk free from adulterants. These findings also supported the previous study of determining possibility of adulteration through physical and chemical quality parameters which showed adulteration possibility of around 76.6% [12].

CONCLUSIONS

The Poly glycol and Poly ethylene glycol are effective permeation enhancers to be used in combination and the CCM gel formulations can be effectively used because even when taken in modest amounts, cefixime trihydrate is quickly absorbed via the skin or membrane since it is freely soluble in methanol. Despite being easily soluble in both methanol and water, CPM can exhibit significant effects when combined with organic solvents. Especially, considering joint and acne infections, the oral formulation is not helpful in patients with ulcers. In order to overcome this problematic situation, CCM gel can be used effectively by direct application on topical infections.

Authors Contribution

Conceptualization: SR, A, FS, AQ
Methodology: AH, SB
Formal analysis: HT, MUIK
Writing-review and editing: AQ, MD, SJ, MH

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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